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Highly Efficient Synthesis of Functionalized Indolizines and Indolizinones by Copper-Catalyzed Cycloisomerizations of Propargylic Pyridines

Bin Yan, Yebing Zhou, Hao Zhang, Jingjin Chen, and Yuanhong Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

yhliu@mail.sioc.ac.cn

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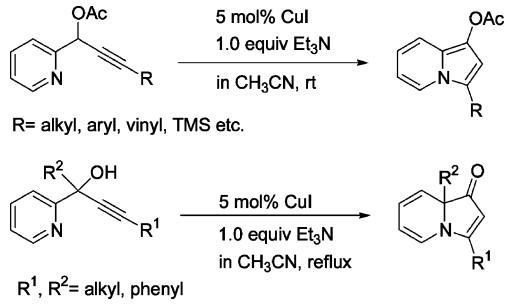
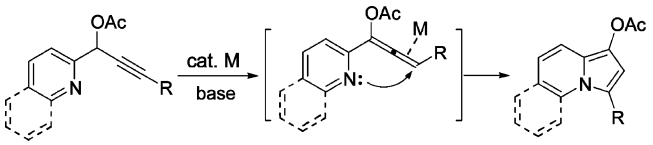


The copper-catalyzed cycloisomerizations of 2-pyridyl-substituted propargylic acetates and its derivatives are described, which offer an efficient route to C-1 oxygenated indolizines with a wide range of substituents under mild reaction conditions. The presented method could be readily applied to the synthesis of indolizinones through a cyclization/1,2-migration of tertiary propargylic alcohols.

Indolizines, which exhibit intriguing molecular structures featured by an N-bridgehead bicyclic ring system, have received much attention in recent years.[1] Many of the synthetic and natural indolizines have displayed important biological activities which can find a variety of applications in pharmaceutical use.[2] They are also useful in the field of material science owing to their unique photophysical properties.[3] Although a number of methods are available for the synthesis of indolizines,[4,5] the development of general and efficient synthesis of functionalized indolizines is still highly attractive.[6,7] Recently, Gevorgyan et al. reported an interesting Au-catalyzed cascade 1,2-migration/cycloisomerization of propargylic substrates to indolizines with various functionalities.[8] The metal salts employed were suggested to facilitate an alkyne−vinylidene isomerization with concomitant 1,2-migration of H, silyl, stannyl, or germyl groups by the formation of gold−vinylidene intermediates. We have reported a Pd/Cu-catalyzed one-pot synthesis of 3-aminoindolizines through the reactions of propargyl amines or amides with heteroaryl bromides.[9] It was found that this reaction was strongly dependent on the presence of a base and on the solvent employed. A suitable base may facilitate a propargyl−allenyl isomerization to an allenic intermediate or serve as a good ligand to stabilize the copper intermediates. On the basis of this work, we envisioned that propargylic acetates bearing pyridine rings may also undergo copper-catalyzed cyclization via allenic intermediates to give indolizines (Scheme 1). In this paper, we report the cyclization of 2-pyridyl-substituted propargylic acetates **1** by a more convenient, economic, and efficient copper-catalyzed approach for the synthesis of C-1 oxygenated indolizines at room temperature. The present method could be readily

SCHEME 1



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(7) During our manuscript preparation, a platinum or $InCl_3$-catalyzed cyclization of pyridine propargylic pivaloate and its derivatives to indolizines and indolizinones was been reported by Sarpong et al. The reaction usually requires higher temperature (40−70 °C for indolizines and 100 °C for indolizinones) with benzene as the solvent and bulky electron-rich phosphine ligands such as 2-(di-*tert*-butylphosphino)biphenyl or 2-(dicyclohexylphosphino)biphenyl as the ligands in the case of platinum catalysis. See: Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169.

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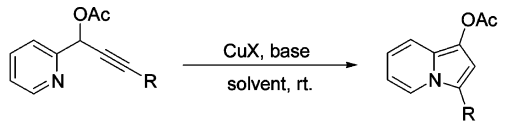
TABLE 1. Optimization Studies for the Cu-Catalyzed Cycloisomerization Reactions



1a, R=Bu; **1b**, R=H — **2a**, R=Bu; **2b**, R=H

entry	substrate	CuX	base	solvent	time	product	yield[a] (%)
1	**1a**	5% CuI	−	THF	3 h	**2a**	98
2	**1a**	5% CuI	2.0 Et_2NH	THF	1.5 h	**2a**	95
3	**1a**	5% CuI	−	CH_2Cl_2	3.5 h	**2a**	(>99)
4	**1a**	5% CuBr	−	CH_3CN	2 h	**2a**	(>99)
5	**1a**	5% CuCI	−	CH_3CN	3 h	**2a**	(>99)
6	**1a**	2% CuI	−	CH_3CN	6 h	**2a**	(>99)
7	**1a**	5% CuI	−	CH_3CN	2 h	**2a**	97
8	**1a**	5% CuI	1.0 Et_3N	CH_3CN	40 min	**2a**	97
9	**1a**	−	2.0 Et_3N	CH_3CN	12 h	**2a**	NR[b]
10	**1b**	5% CuI	−	CH_3CN	18 h	**2b**	63
11	**1b**	5% CuI	1.0 Et_3N	CH_3CN	2 h	**2b**	82

[a] Isolated yields; NMR yields are given in parentheses. [b] NR = no reaction.

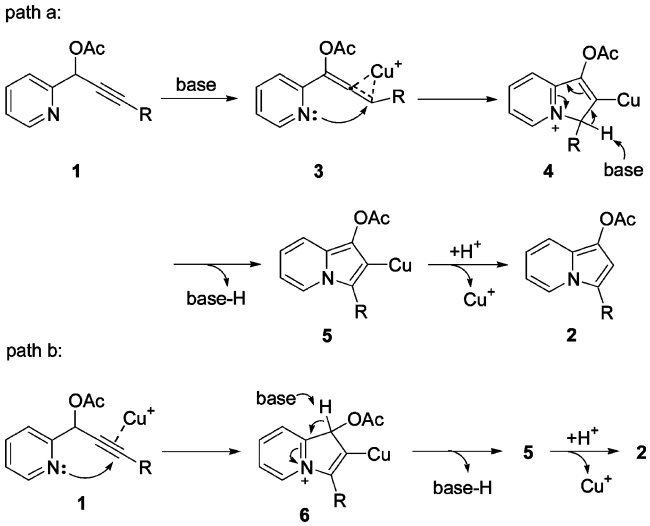
applied to the synthesis of indolizinones through a cyclization/1,2-migration of tertiary propargylic alcohols.

To test the hypothesis, the cyclization of propargyl acetates **1a** and **1b**, which were easily prepared in good yields from pyridine-2-carboxaldehyde, were examined first, and the results are summarized in Table 1. Gratifyingly, the reaction was proved to be quite efficient with various copper catalysts. In the presence of 5 mol % of CuI, the cyclization occurred smoothly in THF to afford the desired indolizine **2a** in 98% yield after 3 h without the use of any base (Table 1, entry 1).

When a base such as Et_2NH was added, the reaction proceeded much faster, furnishing **2a** in 95% yield within 1.5 h (Table 1, entry 2). Further studies indicated that the amine played a role in increasing the reaction rate (Table 1, entries 7, 8, 10, and 11). Importantly, when terminal alkyne **1b**[10] was reacted in CH_3CN, a complete conversion of the starting material was observed after 18 h without the amine and in 2 h with 1.0 equiv of Et_3N present. Additionally, the final yield of product was 63% without the amine and 82% with the amine present. No reaction was observed in the absence of Cu(I) at room temperature (Table 1, entry 9).[11] On the basis of the results shown above, we chose the following reaction conditions: 5 mol % of CuI, 1.0 equiv of Et_3N in CH_3CN, stirred at room temperature for an appropriate time.

Under these conditions, a variety of propargylic compounds bearing pyridine rings was smoothly converted into the corresponding indolizines or its analogues (Table 2), which indicated the procedure readily accommodates a wide range of functionalities. The alkyne moiety in propargylic pyridine **1** bearing an aromatic ring reacted very well to provide the cyclization products in 87−97% yields within less than 15 min (Table 2, entries 1−4). Electron-withdrawing as well as electron-donating substituents on aromatic rings are well tolerated. The use of sterically more hindered ^{t}Bu-substituted **1g** also proceeded to afford **2g** in 90% yield after 1 h (Table 2, entry 5). The appearance of a vinylic group in the substrates such as **1h** and **1i** did not influence the efficiency of this reaction, in which the corresponding products **2h** and **2i** were formed in 86 and 83% yields, respectively (Table 2, entries 6 and 7). An alkyne terminus tethered with an OAc group afforded the corresponding product **2j** in 90% yield (Table 2, entry 8). Alkyne substituted with a TMS group resulted in a complete desilylation during the reaction, and the product **2b** was obtained in 68% yield (Table 2, entry 9). 6-Bromopyridyl-substituted substrate **1l** afforded the desired indolizine **2k** in 77% yield (Table 2, entry 10). The reaction of 2-quinolyl-substituted propargyl acetate **1m** also proceeded well to give benz[*e*]indolizine **2l** in 89% yield (Table 2, entry 11). It is interesting to note that the reaction has also been accomplished starting from **1n** with silyl-protected groups (OTBS-), furnishing **2m** in 85% yield (Table 2, entry 12). A clean formation of a phenyl-bridged indolizine **2n** was achieved in 82% yield by using **1o** as the substrate (Table 2, entry 13). The structure of indolizines was unequivocally confirmed by single-crystal analysis of **2l**,[12] and the result clearly showed N-bridgehead bicycles.

SCHEME 2



We propose the following two possible pathways for the formation of indolizine **2** (Scheme 2). According to path a, a CuI-base-induced propargyl−allenyl isomerization of **1** occurs first to form **3**. Next, nucleophilic attack of pyridyl nitrogen to the Cu-coordinated allenyl double bond results in the formation of cation **4**; this is followed by deprotonation to lead to copper(I)−indolizine intermediate **5**. Protonolysis of **5** with loss of Cu(I) affords the desired product **2**. This mechanism is analogous to that proposed for Cu-catalyzed cycloisomerization of alkynyl imines into pyrroles[5o] and silver-assisted cyclization of allenyl ketones to furans.[13] Alternatively, in path b,[7] coordination of the triple bond in alkyne **1** to Cu(I) enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack of the nitrogen lone pair would form the cation **6**, which undergoes deprotonation followed by demetalation to afford **2**.

To probe that Cu(I) could be an effective catalyst for inducing a cyclization/1,2-shift of tertiary propargylic alcohol reported

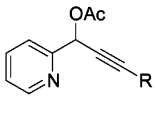
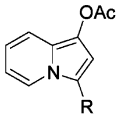
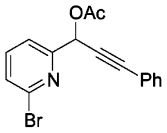
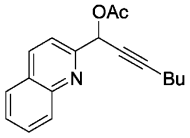
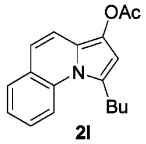
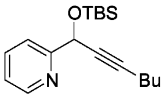
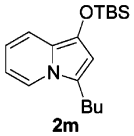
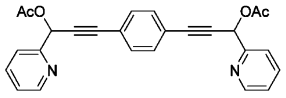
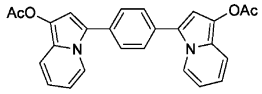
(10) It was reported that employment of Cu(I) salts for the cyclization of TBS-protected propargyl pyridine 2-[1-(*tert*-butyldimethylsilyl)prop-2-ynyl] pyridine led to trace amount of products. See ref 8.

(11) It was found that, under solvent-free conditions, **1a** can be cyclized without copper catalyst to afford **2a** in 41% yield after 8 h at high temperature of 130 °C.

(12) See Supporting Information.

(13) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.

TABLE 2. Copper-Catalyzed Cycloisomerizations of Propargylic Pyridines to 1,3-Disubstituted Indolizines

entry	propargylic substrates		time	product	yield(%)[a]
					
1	R = Ph	(**1c**)	15 min	**2c**	89
2	R = 4-MeOC$_6$H$_4$	(**1d**)	10 min	**2d**	92
3	R = 4-ClC$_6$H$_4$	(**1e**)	15 min	**2e**	87
4	R = 1-naphthyl	(**1f**)	15 min	**2f**	97
5	R = ^{t}Bu	(**1g**)	1 h	**2g**	90
6	R = 1-cyclohexenyl	(**1h**)	30 min	**2h**	86
7	R = (*E*)-CH=CHPh	(**1i**)	20 min	**2i**	83
8	R= CH$_2$CH$_2$OAc	(**1j**)	1 h	**2j**	90
9	R= TMS	(**1k**)	16 h	**2b**	68
10		(**1l**)	3 h	 **2k**	77
11		(**1m**)	10 min	 **2l**	89
12		(**1n**)	2 h	 **2m**	85
13	 (**1o**)		30 min	 **2n**	82[b]

[a] Isolated yields. All of the reactions were carried out at room temperature using 5 mol % of CuI, 1 equiv of Et_3N in CH_3CN. [b] 10 mol % of CuI and 2.0 equiv of Et_3N were used.

by Sarpong,[7] we proceeded to examine the cyclizations of **7**. To our delight, our method showed great efficiency for the 1,2-migration reactions. As shown in Table 3, under refluxing conditions in CH_3CN, a variety of propargylic alcohol was successfully transferred to indolizinones **8a**−**f** in the presence of 5 mol % of CuI and 1 equiv of Et_3N within 3 h, and the yields ranged from 70 to 92%. According to the reported method catalyzed by $PtCl_2$, a higher reaction temperature (100 °C in benzene) and longer reaction time (48−168 h) were needed. We also investigated the reaction in the absence of a base, and the results indicated that comparable yields of migration products were observed (Table 3, entries 1−5); however, in some cases, a longer reaction time was required (Table 3, entries 4 and 5).

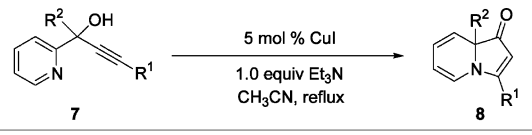
In summary, we have developed a Cu-catalyzed cycloisomerization or cyclization/1,2-migration of propargylic pyridines under mild reaction conditions, which provided an efficient route to C-1 oxygenated indolizines and indolizinones with a wide range of substituents. Further studies to extend the scope of synthetic utility for these Cu-catalyzed cyclizations are in progress in our laboratory.

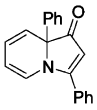
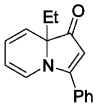
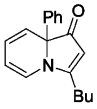
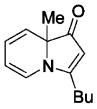
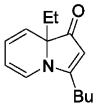
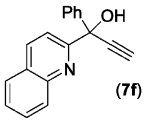
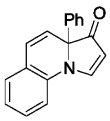
Experimental Section

General Procedure for the Synthesis of C-1 Oxygenated Indolizines. To a solution of propargylic acetate **1** (0.5 mmol) in 3 mL of acetonitrile were added CuI (4.8 mg, 0.025 mmol) and triethylamine (70 μL, 0.5 mmol) successively at room temperature. The resulting solution was stirred at room temperature until the reaction was completed as monitored by thin-layer chromatography. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography on silica gel to afford the desired products **2**. Note: The color of most indolizines **2** turned from yellow to brown when exposed in air for several hours.

Acetic Acid 3-Butylindolizin-1-yl Ester (2a). Flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:10)

TABLE 3. Copper-Catalyzed Cyclization/1,2-Migration of Tertiary Propargylic Alcohols



entry	R^1	R^2		time	product		yield (%)[a,b]
1	Ph	Ph	(**7a**)	2 h		**8a**	76 (2 h, 78)
2	Ph	Et	(**7b**)	2h		**8b**	86 (2 h, 84)
3	Bu	Ph	(**7c**)	1 h		**8c**	86 (1 h, 84)
4	Bu	Me	(**7d**)	3 h		**8d**	70 (5 h, 67)
5	Bu	Et	(**7e**)	1h		**8e**	92 (3.5 h, 91)
6			(**7f**)	1.5 h		**8f**	71

[a] Isolated yields. Unless noted, all of the reactions were carried out at refluxing temperature using 5 mol % of CuI, 1 equiv of Et_3N in CH_3CN. [b] The reactions were done in the absence of Et_3N, and the results of these reactions (reaction time and the yields of the products) are listed in the parentheses.

afforded the title product in 97% isolated yield as a light yellow liquid: ^{1}H NMR (C_6D_6, Me_4Si) δ 0.78 (t, J = 7.2 Hz, 3H), 1.12−1.24 (m, 2H), 1.35−1.45 (m, 2H), 1.86 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 6.07−6.12 (m, 1H), 6.32−6.37 (m, 1H), 6.80 (s, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.30−7.34 (m, 1H); ^{13}C NMR (C_6D_6, Me_4Si) δ 14.0, 20.4, 22.8, 25.5, 29.4, 105.3, 110.0, 114.5, 116.5, 121.1, 121.3, 121.7, 127.3, 168.3; IR (neat) 2957, 1748, 1556, 1212, 1081, 731 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1259.

A Typical Procedure for the Synthesis of 3,8a-Diphenyl-8a*H*-indolizin-1-one (8a). To a solution of 1,3-diphenyl-1-(pyridin-2-yl)prop-2-yn-1-ol **7a** (143 mg, 0.5 mmol) in 3 mL of acetonitrile were added CuI (4.8 mg, 0.025 mmol) and triethylamine (70 μL, 0.5 mmol) successively at room temperature. The resulting solution was stirred at refluxing temperature until the reaction was completed as monitored by NMR (2 h) (the reactions of other substrates were monitored by GC). The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether 1:4) to afford the product **8a** in 76% isolated yield as a deep yellow solid: mp 120−122 °C; ^{1}H NMR (C_6D_6, Me_4Si) δ 4.92 (t, J = 6.6 Hz, 1H), 5.08 (s, 1H), 5.67 (dd, J = 9.3 Hz, J = 5.4 Hz, 1H), 6.31 (d, J = 7.2 Hz, 1H), 6.43 (d, J = 9.0 Hz, 1H), 6.96−7.11 (m, 6H), 7.21 (t, J = 7.8 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H); ^{13}C NMR (C_6D_6, Me_4Si) δ 72.1, 99.9, 108.9, 122.8, 122.8, 124.6, 125.0, 128.0, 128.1, 128.8, 129.0, 129.7, 130.8, 141.5, 173.9, 199.9; IR (KBr) 3059, 1684, 1541, 1385, 761, 697 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{15}NO$ 285.1154, found 285.1164.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds and CIF file giving crystallographic data of **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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